



16955DIVCONCIP(AP)PATENT

UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:
Woodward et al

Serial No: 08/605,567

Filed: February 22, 1996

For: CYCLOPENTANE HEPTANOIC
ACID, 2-CYCLOALKYL OR
ARYLALKYL DERIVATIVES AS
THERAPEUTIC AGENTS

Group No. : 1209

Examiner: M. Cebulak

DECLARATION UNDER 37 CFR 1.131

Honorable Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Dear Sir:

The Declarant hereby declares as follows:

THAT, he is currently employed by Allergan, Inc. in the
Department of Biological Sciences, Pharmaceutical Research &
Development;

THAT, he has been employed at Allergan since 1982;

THAT, his research is in the field of glaucoma, in
particular the effect of prostaglandin derivatives on
lowering intraocular pressure, among other fields;

THAT, he obtained a Ph.D. degree (Pharmacology) from
CNAa, Leicester School of Pharmacy 1980;

THAT, he obtained a B.S. (Pharmacology) in 1975;

THAT, he is named as an inventor in the above-identified patent application;

THAT, he directed and supervised the following experiments, in the United States of America, prior to August 3, 1993, the filing date of U.S. Patent Number 5,510,383 to Bishop;

THAT, as described in Example 6, of U.S. Patent Number 5,352,708, i.e. the parent application of the present application, the effectiveness of AGN 192185 in lowering intraocular pressure (IOP) in dogs was measured;

THAT, AGN 192185 is the 1-CONH₂ derivative of fluprostenol;

THAT, as shown in Exhibit A, which is a true copy of page 85 of his Notebook (with only the dates blocked out) and is attached hereto and made a part hereof, a 0.1% solution of AGN 192185 in a vehicle was prepared and designated as 185B;

THAT, as shown in Exhibit B, which is a true copy of page 86 of his Notebook (with only the dates blocked out) and is attached hereto and made a part hereof, 185B was topically applied to one eye of eight dogs and the lowering of IOP in that eye over 24 hours was measured;

THAT, in Dog Numbers KHD2, KID2, AC2 and KLC2 the IOP in the eye that received 185B was lowered;

THAT, as shown in a graph format in Exhibit C, which is a true copy of page 20 of his Notebook (with only the dates blocked out) and is attached hereto and made a part thereof, 0.01% fluprostenol when tested as described in Example 6 of U.S. Patent Number 5,352,708 also shows a lowering of the IOP in dogs;

THAT, as shown in a graph format in Exhibit D, which is a true copy of page 15 of his Notebook (with only the dates blocked out) and is attached hereto and made a part thereof, 0.1% fluprostenol when tested as described in Example 6 of U.S. Patent Number 5,352,708 also shows a lowering of IOP in dogs;

THAT, the results reported in Exhibits A through D clearly demonstrate that topical administration of fluprostenol and derivatives thereof lower IOP;

The undersigned declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Respectfully,

4.23.97

Date


David F. Woodward

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EXHIBIT A

Title IOP - DOGS

Project Name _____

Project No. _____

Enter Purpose, Method, Results and
Conclusions for each Study.

Date _____

Sample I.D. No. _____

Book No. _____

Continued from _____

Purpose: see page 9.Method: see pages 1-9.Drug Preparation: see page 9.Drug Code: C. 17 = AGN. 192185
185A = vehicle
185B = drugRabbit Test: rabbit = 27 @ eye
2 = 30 min. eye clear + rabbit in good healthNotes:

OSH

.75

1.0

1.25

.50

1.0

.50

.75

.75

6.5/8 = .81

Study done on 11/2/92

DOG KID₂ was + 2.5 - had swellingDOG AC₂ had severe ptosis

Continued on 86

Signature Linda WilliamsRead & Understood by Jan Beltranda
Date _____

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Title _____

Project Name _____

Project No. _____

Enter Purpose, Method, Results and
Conclusions for each Study.

Date _____

Sample I.D. No. _____

Book No. _____

Continued from _____

| Dog Number | Eye | T=0 IOP \pm SD | T=2 IOP \pm SD | T=4 IOP \pm SD | T=6 IOP \pm SD | T=24 IOP \pm SD |
|------------|-------|------------------|------------------|------------------|------------------|-------------------|
| (A) 2002 | L | 12.0 \pm .3 | 15.6 \pm .6 | 13.4 \pm .5 | 11.4 \pm .4 | 14.2 \pm .7 |
| | (P) R | 13.1 \pm .2 | 13.6 \pm .6 | 14.3 \pm .6 | 10.1 \pm 1.0 | 14.6 \pm .6 |
| KHD2 | L | 12.7 \pm .4 | 17.0 \pm .4 | 15.1 \pm .8 | 14.2 \pm .1 | 14.7 \pm .7 |
| | (R) R | 12.5 \pm .1 | 7.2 \pm .7 | 8.8 \pm .5 | 10.7 \pm .7 | 10.9 \pm .1 |
| KID2 | L | 13.5 \pm .1 | 12.8 \pm .5 | 13.3 \pm .9 | 14.0 \pm .2 | 10.1 \pm .3 |
| | (R) R | 13.4 \pm .1 | 7.8 \pm .1 | 7.1 \pm .6 | 11.2 \pm .1 | 7.8 \pm .5 |
| KUD2 | L | 13.7 \pm .3 | 14.9 \pm .6 | 12.0 \pm .3 | 12.9 \pm .2 | 13.3 \pm .9 |
| | (R) R | 16.2 \pm .4 | 14.3 \pm .1 | 12.8 \pm .3 | 13.9 \pm .3 | 16.1 \pm .7 |
| KPC2 | L | 15.3 \pm .7 | 18.3 \pm .3 | 16.6 \pm .2 | 12.6 \pm .2 | 18.4 \pm .5 |
| | (R) R | 18.5 \pm .6 | 15.1 \pm .8 | 14.0 \pm .7 | 16.8 \pm .6 | 13.1 \pm .2 |
| ACL2 | L | 18.5 \pm .7 | 18.5 \pm .5 | 16.8 \pm .5 | 20.1 \pm .8 | 17.1 \pm .6 |
| | (R) R | 18.4 \pm .7 | 15.7 \pm .1 | 13.4 \pm .6 | 13.4 \pm .7 | 15.5 \pm .1 |
| KLCL | L | 15.5 \pm .7 | 18.4 \pm .1 | 18.7 \pm .4 | 17.7 \pm .6 | 15.5 \pm .3 |
| | (R) R | 15.9 \pm .6 | 14.4 \pm .7 | 15.2 \pm .3 | 13.2 \pm .3 | 12.8 \pm .2 |
| TPCL | L | 16.6 \pm .6 | 15.9 \pm .3 | 14.2 \pm .3 | 12.7 \pm .9 | 12.0 \pm .7 |
| | (R) R | 14.6 \pm .9 | 15.5 \pm .7 | 16.8 \pm .8 | 13.7 \pm .5 | 13.2 \pm .3 |

Behrman account general VAX

AR102210015 228 x 20

0.1A ACM192185

0 1 0.00 2 2.00 3 4.00 4 6.00 5 24.00

| | | | | | |
|----|-------|--------|-------|-------|-------|
| 1 | 15.53 | 12.81 | 13.09 | 12.70 | 12.54 |
| 2 | 2.33 | 3.72 | 2.31 | 2.30 | 2.91 |
| 3 | 0.95 | 1.41 | 1.10 | 0.87 | 1.10 |
| 4 | 14.53 | 15.83 | 14.50 | 14.01 | 14.23 |
| 5 | 2.06 | 1.96 | 1.43 | 2.82 | 2.59 |
| 6 | 0.74 | 0.74 | 0.55 | 0.99 | 0.70 |
| 7 | 0.00 | -2.712 | -3.44 | -2.82 | -2.67 |
| 8 | 0.00 | 2.24 | 2.40 | 1.20 | 2.74 |
| 9 | 0.00 | 0.55 | 0.91 | 0.45 | 1.03 |
| 10 | 0.00 | -3.12 | -3.26 | -3.22 | -2.53 |
| 11 | 0.00 | 1.41 | 0.11 | -0.45 | -0.11 |
| 12 | 0.00 | 0.74 | 1.41 | 1.77 | 2.43 |
| 13 | 0.00 | 0.95 | 0.41 | 0.94 | 1.00 |
| 14 | 0.00 | 1.41 | 0.11 | -0.45 | -0.11 |
| 15 | 0.00 | -2.712 | -3.44 | -2.82 | -2.67 |
| 16 | 0.00 | 2.24 | 2.40 | 1.20 | 2.74 |
| 17 | 0.00 | 0.55 | 0.91 | 0.45 | 1.03 |
| 18 | 0.00 | -3.12 | -3.26 | -3.22 | -2.53 |

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Signature Jan Behrman

Read & Understood by

Date

Jan Behrman

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EXHIBIT C

Title

Project Name

Project No.

Enter Purpose, Method, Results and
Conclusions for each Study.

Date

Sample I.D. No.

Book No.

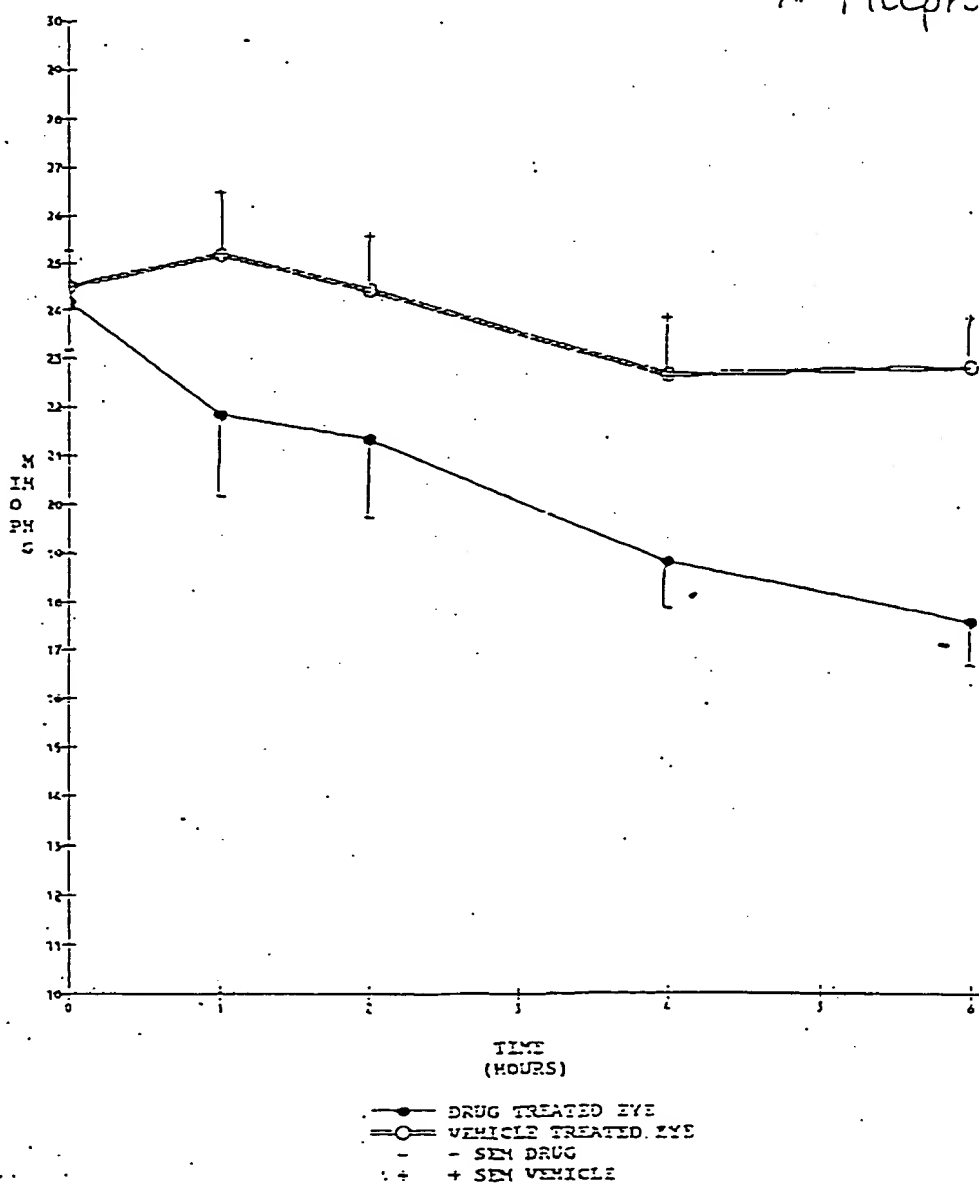
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03-OCT-91 18:19 Page 1

925AB DOGS N=6

0.01% Fluorostencol



Continued on

Signature

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Linda Williams

Read & Understood by

Date

Linda Williams

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EXHIBIT D

Title _____
Project Name _____
Project No. Same as pg 13
Enter Purpose, Method, Results and
Conclusions for each Study.

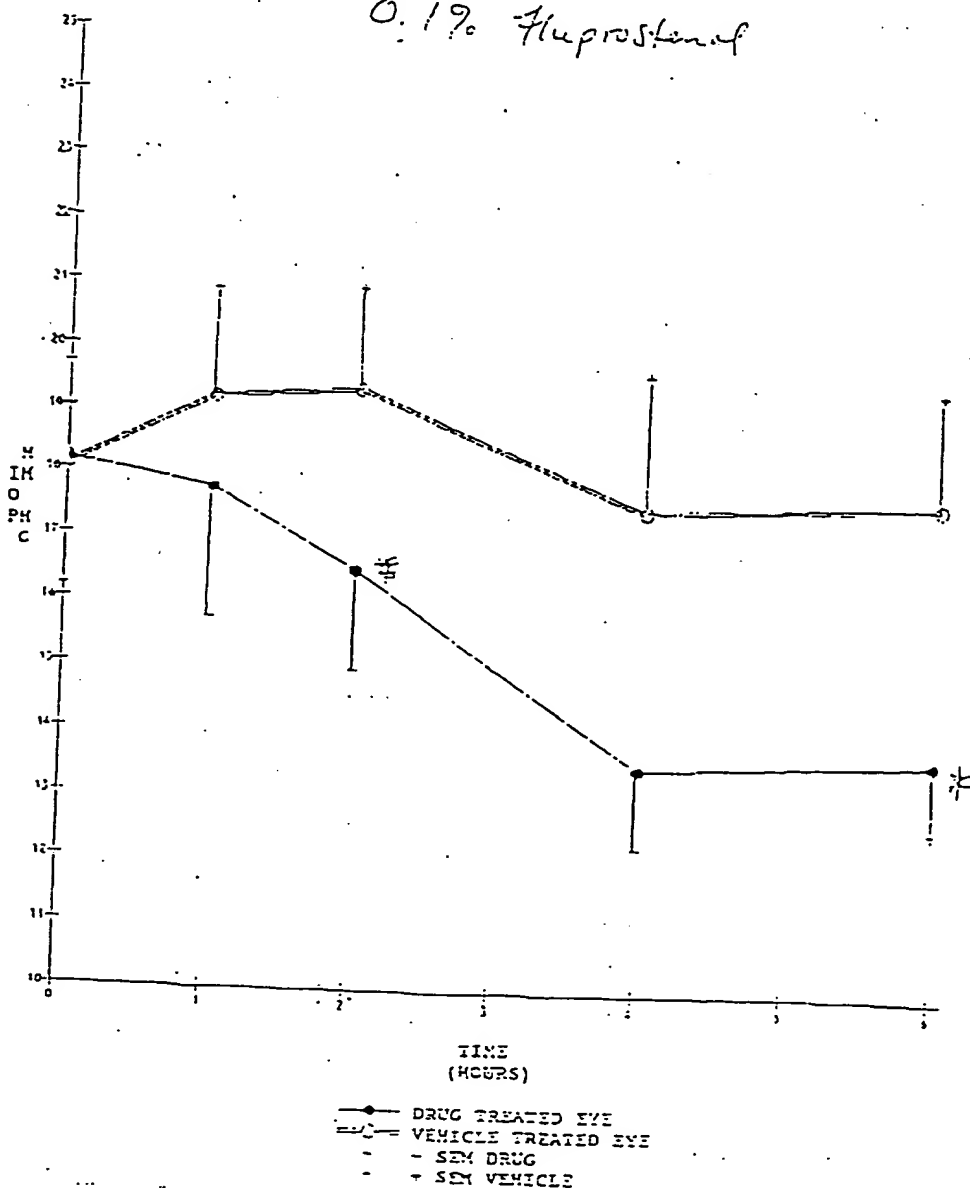
Date _____
Sample I.D. No. _____
Book No. _____
Continued from _____

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28-SEP-91 13:30 Page 1

DOG IOP 924

0.1% Fluprostenal



n=5

CSW

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Continued on pg 16
Signature Jan Behrends
Date _____

Read & Understood by Linda Williams
Date _____